



Agency for Healthcare Research and Quality
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Evidence-based Practice Center Systematic Review Protocol

Project Title: Fractional Exhaled Nitric Oxide Clinical Utility in Asthma Management

I. Background and Objectives for the Systematic Review

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.¹ In the United States (US), the current prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.0 million Americans in 2014.^{2,3} Asthma can significantly impact patients' and families' quality-of-life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.⁴ In the US, asthma contributes significantly to healthcare resource utilization and associated costs. For example, in 2012, asthma was one of the top twenty leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. While the severity of disease varies between patients and over time in the same patient, asthma can be fatal, accounting for approximately 1 death per 100,000 Americans.⁵

The diagnosis of asthma is challenging. The common symptoms such as shortness of breath, wheezing, and cough, are relatively non-specific. Various tests, including spirometry pre and post bronchodilator, and bronchoprovocation may be used by clinicians to diagnose asthma. However, the diagnosis remains clinical; there is no single gold standard diagnostic test. More recently, fractional exhaled nitric oxide (FeNO) has been added to the list of tests clinicians may use to diagnose or manage asthma.

Nitric oxide is a gas normally found in each exhaled breath in all humans. It is measured as the FeNO, requiring a steady exhalation into a device for measurement. Patients with asthma have increased levels of inducible nitric oxide synthase (iNOS2), the enzyme that produces NO in their airway epithelium. Therefore, it is not surprising that FeNO has been found to be elevated in patients with atopic asthma.⁶ However, an inflammatory role for nitric oxide in asthma has also been suggested, particularly with eosinophilic inflammation.^{7,8} FeNO provides an additional diagnostic test that may be used to support the diagnosis of asthma as well as monitor the disease activity (inflammation) and the response to asthma treatment.

In young children with asthma, the diagnosis of asthma is challenging, given their inability to participate in the usual diagnostic testing. One potential use of FeNO is to predict which children who have repeated episodes of wheezing are likely to be diagnosed with asthma later in childhood. There are some data⁹⁻¹¹ to suggest that FeNO compares favorably to other predictive tests to address the challenges in such children.

In individuals who have been diagnosed with asthma, FeNO may be useful to assess which treatments are likely to be most helpful to a given patient^{12,13} and/or to follow the response to treatment. Ascertaining whether a patient has 'responded' to a given

therapeutic can be difficult given the inherent variability in the disease, the non-specific nature of many measures of response, and the time required to demonstrate an effect of treatment. In addition to have some possible advantages over other tests to select treatment and measure response to treatment, as an inflammatory marker, FeNO may also identify patients in whom non-compliance with anti-inflammatory medications (such as inhaled corticosteroids) may be an issue.¹⁴

Multiple factors limit the interpretation of FeNO data and its utility including asthma phenotype, tobacco, inhaled or oral corticosteroids, bronchodilators, patient weight, patient age, fasting state or food intake, or prior use of mouthwash. Moreover, the criteria for what constitutes a clinically significant change in FeNO remains uncertain.

Purpose of the Systematic Review

In 1989, the National Heart, Lung and Blood Institutes (NHLBI) initiated the National Asthma Education and Prevention Program (NAEPP) to address growing concern about asthma in the US. One of the first accomplishments of the NAEPP was to convene a panel of experts who produced a report, National Asthma Education and Prevention Program Expert Panel Report (EPR): Guidelines for the Diagnosis and Management of Asthma, in 1991. The guidelines address the diagnosis, evaluation, and treatment of asthma. Given the most recent report, EPR-3, was published in 2007,¹ NHLBI assessed the need for an update by requesting information from the public, NAEPP Coordinating Committee Members and its affiliates, and members of the 2007 Expert Panel. Collected information was provided to the NHLBI Advisory Council Asthma Expert Working Group, which produced a report to summarize the process and recommendations from their needs assessment.¹⁵ The Working Group identified six high priority topics that should be updated. For each topic, key questions meriting a systematic literature review were formulated. NHLBI engaged AHRQ to perform the systematic reviews through its Evidence-based Practice Centers (EPC). This document represents the systematic review of “The Role of FeNO in the diagnosis and treatment of asthma”. The review also will highlight areas of controversy and identify needs for future research on this priority area.

II. The Key Questions

KQ1: What is the clinical utility of FeNO measurements in the management of asthma in addition to, or instead of, other tests that might be performed? Specifically,

1.a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?

1.b: What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 and older?

1.c: What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 and older?

1.d: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 and older?

1.e: In children ages 0-4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 and above?

Population, Interventions, Comparators, Outcomes, Timings, and Settings (PICOTS) by Key Question (KQ)

Population(s)

KQ 1.a: Ages 5 years and older suspected to have asthma, especially those who experience wheezing with respiratory tract infections.

KQ 1.b: Ages 5 years and older with asthma (all levels of severity)

KQ 1.c: Ages 5 years and older with asthma (all levels of severity)

KQ 1.d: Ages 5 years and older with asthma (all levels of severity)

KQ 1.e: Ages 0-4 years with recurrent wheezing episodes at the time of testing but outcome ascertained at age 5 or older

Interventions

FeNO measurement (one-time or multiple measurements, cross sectional/ point of care or longitudinal measurements).

Comparators

KQ 1.a: Standard diagnostic testing of asthma made by healthcare providers based on history, clinical course and the available tests (spirometry, hyperresponsiveness to SABA, methacholine challenge Sputum eosinophils; Peripheral blood eosinophils; peak flow)

KQ 1.b: Standard monitoring methods of asthma made by healthcare providers based on history, clinical course and the available tests (spirometry, peak flow, assessment of symptoms using questionnaires (e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT))

KQ 1.c: Selection of medications by healthcare providers based on history, clinical course and the available tests (Blood eosinophils, induced sputum, bronchialveolar lavage, allergy tests (skin testing, serum allergen specific IgE))

KQ 1.d: Response to treatment as determined by healthcare providers based on history, clinical course and the available tests (spirometry, peak flow, assessment of symptoms using questionnaires (e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT))

KQ 1.e: Asthma Predictive Index and its components

Outcomes

KQ 1.a: Diagnostic accuracy measures (Sensitivity and specificity, positive and negative predictive values, likelihood ratios of a positive and negative test)

KQ 1.b, KQ 1.c, and KQ 1.d:

- Asthma control composite scores
 - Asthma Control Test (ACT)
 - Asthma Control Questionnaire (ACQ)
- Exacerbations
 - Systemic corticosteroids for asthma
 - Asthma specific hospitalizations
 - Asthma-specific ED visits (separate urgent care visits when they can be differentiated)
 - Asthma specific ICU admission/intubations
 - Death (all causes and asthma related)
- Healthcare utilization and costs
 - Asthma-specific hospitalization
 - Asthma-specific emergency department visits (separate urgent care visits when they can be differentiated)
 - Asthma specific outpatient visits
 - Asthma-specific detailed medication use (name, dose, duration)
 - Resource use related to the intervention (personnel time and equipment)
- Spirometry
- Asthma- specific quality of life - Asthma Quality of Life Questionnaire (AQLQ); Pediatric Asthma Quality of Life Questionnaire (PAQLQ); Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire (PACQLQ)
- Adherence to treatment as detected by FeNO testing

KQ 1.e:

- Incidence of asthma for children ages 5 and above
- Positive predictive value for children ages 5 and above
- Negative predictive for children ages 5 and above

KQ1 a-e:

- Any reported adverse effects to testing

Timing

Studies with any duration of follow up will be included. However, follow-up duration will be considered as a covariate in the analyses.

Settings

Outpatient and hospital settings.

Study type

KQ 1.a and KQ 1.e:

- Included: RCTs, cohort or comparative effectiveness, cross sectional, case reports (for harms)

- Excluded: surveys, narrative reviews, editorials, letters, or erratum, qualitative research, in vivo, in vitro, and animal studies

KQ 1.b, KQ 1.c, and KQ 1.d:

- Included: RCTs, cohort or comparative effectiveness, case reports (for harms)
- Excluded: Cross-sectional, surveys, narrative reviews, editorials, letters, or erratum, qualitative research, in vivo, in vitro, and animal studies

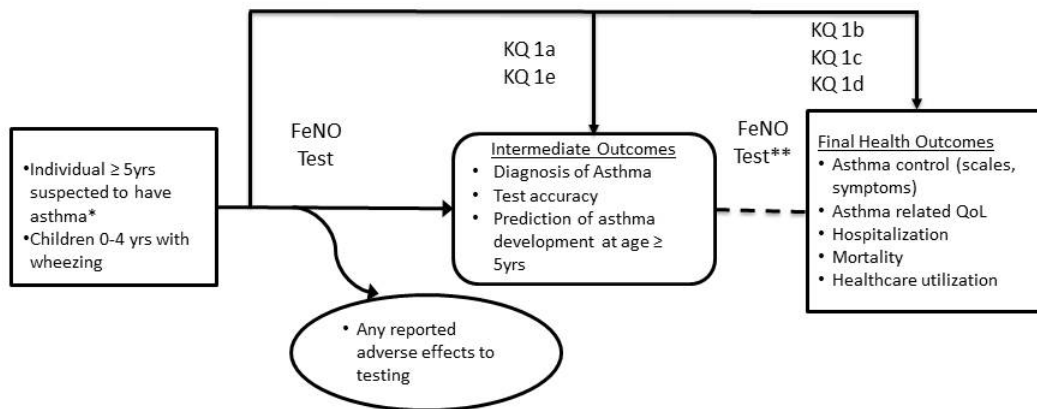
Subgroups

- Robustness of “gold standard” used in the literature
- Tobacco use
- Asthma phenotype (eosinophilic, neutrophilic, paucicellular)
- Use of inhaled/oral corticosteroids prior to FeNO testing
- Use of bronchodilators prior to FeNO testing
- Whether appropriate testing protocol was followed (alcohol consumption, fasting state or food intake, prior use of mouthwash)
- BMI/weight
- Manufacturer/device model (chemiluminescence, electrochemical methods)
- Exhalation flow rate
- Age (age 0-4, 5-11, 12 and above)

III. Analytic Framework

Figure 1. Provisional analytic framework

Analytic framework. Fractional Exhaled Nitric Oxide Clinical Utility in Asthma Management.



*Primarily individuals with wheezing & respiratory tract infection although some may not have wheezing

**The purpose of a FeNO Test performed after a diagnosis is established would be to monitor disease activity, choose treatment & assess response to treatment

IV. Methods

To conduct this systematic review, the EPC will follow the established methodologies as outlined in the EPC Methods Guide for Comparative Effectiveness Reviews.¹⁶ We sought input from AHRQ Task Order Officers and the Technical Expert Panel regarding the research process, such as literature search strategy, additional relevant literature, analysis plan, and reporting findings.

A. Criteria for Inclusion/Exclusion of Studies in the Review

We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

Table 1. Inclusion and exclusion criteria

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	<ul style="list-style-type: none"> Humans KQ 1.a: <ul style="list-style-type: none"> Ages 5 years and older suspected to have asthma KQ 1.b, KQ 1.c, and KQ 1.d: <ul style="list-style-type: none"> Ages 5 years and older Patient with asthma 	<ul style="list-style-type: none"> Animal Studies

	<p>KQ 1.e:</p> <ul style="list-style-type: none"> • Ages 0-4 years at the time of testing but outcome ascertained at age 5 or older • Patients with recurrent wheezing episodes 	
Interventions	FeNO measurement (one-time or multiple measurements, cross sectional/ point of care or longitudinal measurements)	None
Comparators	<p>KQ 1.a: Standard diagnostic testing of asthma made by healthcare providers based on history, clinical course and the available tests (spirometry, hyperresponsiveness to SABA, methacholine challenge); Sputum eosinophils; Peripheral blood eosinophils; peak flow)</p> <p>KQ 1.b: Standard monitoring methods of asthma made by healthcare providers based on history, clinical course and the available tests (spirometry, peak flow, assessment of symptoms using questionnaires (e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT))</p> <p>KQ 1.c: Healthcare providers history, clinical course and the available tests (Blood eosinophils, induced sputum, bronchalveolar lavage, allergy tests (skin testing, serum allergen specific IgE))</p> <p>KQ 1.d: Healthcare providers history, clinical course and the available tests and standard monitoring methods (spirometry, peak flow,</p>	None

	assessment of symptoms using questionnaires (e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT)) KQ 1.e: Asthma Predictive Index and its components	
Outcomes	<p>KQ 1.a:</p> <ul style="list-style-type: none"> • Sensitivity • Specificity <p>KQ 1.b, KQ 1.c, and KQ 1.d:</p> <ul style="list-style-type: none"> • Asthma control composite scores: • Asthma Control Test (ACT) • Asthma Control Questionnaire (ACQ) • Exacerbations: <ul style="list-style-type: none"> ○ Systemic corticosteroids for asthma ○ Asthma specific hospitalizations ○ Asthma-specific ED visits (separate urgent care visits when they can be differentiated) ○ Asthma specific ICU admission/intubations ○ Death (all causes and asthma related) • Healthcare utilization and costs <ul style="list-style-type: none"> ○ Asthma-specific hospitalization ○ Asthma-specific emergency department visits (separate urgent care visits when they can be differentiated) ○ Asthma specific outpatient visits ○ Asthma-specific detailed medication use (name, dose, duration) ○ Resource use related to the intervention 	None

	(personnel time and equipment) ○ Spirometry ○ Asthma - specific quality of life - Asthma Quality of Life Questionnaire (AQLQ); Pediatric Asthma Quality of Life Questionnaire (PAQLQ); Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire (PACQLQ) • Adherence to treatment as detected by FeNO testing KQ 1.e: • Diagnosis of asthma in children ages 5 and above • Positive predictive value for children ages 5 and above • Negative predictive for children ages 5 and above KQ1 a-e: • Any reported adverse effects to testing	
Timing	Any duration of follow up	No restriction on follow up
Settings	Outpatient and hospital settings	None
Study design	• Any sample size • RCTs, cohort or comparative effectiveness, case reports • Cross-sectional studies (for KQ1.a and KQ1.e) • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro, and in vivo studies • Non-original data (e.g. narrative reviews, editorials, letters, or erratum) • Cross-sectional studies (for KQ1.b-d), surveys • Qualitative studies • Animal studies
Publications	Any language	Non-English abstract
Abbreviations: FeNO = fractional exhaled nitric oxide; KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial		

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We plan to conduct a comprehensive literature search of six databases, including Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R), EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and SciVerse Scopus from databases inception to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We sought inputs from the Technical Expert Panel (TEP) on refining literature search strategy and identifying additional studies. A medical librarian who is not involved in the initial development of the search strategy will review the search strategy. All citations identified through the process will be imported to a reference management system ((EndNote® Version X4; Thomson Reuters, Philadelphia, PA).

To search grey literature, we will search U.S. Food and Drug Administration (FDA) device registration studies, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites.

In addition, we will search relevant systematic reviews and meta-analysis and conduct reference mining of relevant publications to identify additional existing and new literature.

Independent reviewers, working in pairs, will screen the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer will be retrieved for full-text screening. Independent reviewers, again working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus can't be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process. The literature searches will be updated during the Peer Review process, before finalization of the review.

C. Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, interventions, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot-tested by all study team members using 10 randomly selected studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will randomly select studies, review data extraction, and resolve conflicts.

DistillerSR will also be used to create the data extraction form discussed above and facilitate data extraction.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will evaluate the risk of bias of each included study using predefined criteria. For RCTs identified for KQ 1.b, KQ 1.c, and KQ 1.d, we will use Cochrane Risk of Bias tool

to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias.¹⁷ For observational studies (including case reports), we will select appropriate items from the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions).¹⁸ Additional criteria will be adopted from other quality appraisal tools if deemed appropriate. We plan to use QUADAS-2¹⁹ for KQ 1.a and an inventory of items specific to prognosis (14 domains addressing 6 sources of bias related to study participation, study attrition, measurement of prognostic factors, measurement of and controlling for confounding variables, measurement of outcomes, and analysis approaches)²⁰ for KQ 1.e.

E. Data Synthesis

We will qualitatively summarize key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQs.

We will determine whether meta-analysis is appropriate for each KQs based on the similarities of PICOTS presented by the studies.

For clinical utility/harm questions (KQ 1.b, KQ 1.c, and KQ 1.d), we will use the Knapp and Hartung adjustment of the variance.²¹ We will evaluate heterogeneity between studies using I^2 indicator. We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests such as Egger linear regression test if the number of studies is large ($n > 10$).

For diagnostic questions (KQ 1.a and KQ 1.e), we plan to use the symmetric hierarchical summary receiver operating characteristic (HSROC) models to jointly estimate sensitivity and specificity.²² We will back-calculate positive predictive value and negative predictive value from pooled estimates of sensitivity and specificity and present a range of plausible prevalence.²³ Studies may use different cutoff values. We will consult with the TEP to categorize similar cutoff values. Separate meta-analyses will be conducted on each category. We will evaluate heterogeneity between studies using I^2 indicator.

To evaluate publication bias in diagnostic meta-analyses, we will conduct linear regression of log transformed diagnostic odds ratio (logDOR) on inverse root of effective sample size in addition to asymmetry test of funnel plots. P value < 0.10 will be used to detect significance.

To further explore heterogeneity, we plan to conduct subgroup analyses based on factors listed in Section II. We will conduct sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the strength of the body of evidence as per the EPC methods guide on assessing the strength of evidence. We will grade the strength of evidence for the outcomes we classified as most important or critical such as the diagnostic accuracy

measures, asthma control composite scores, exacerbations, mortality, and asthma-specific quality of life. These outcomes are chosen because they are either clinically important from a patient or other stakeholders perspective or highly relevant for decision making (diagnostic accuracy measures).

Grading the SOE will be done for each comparison and for each outcome. For outcomes of efficacy and clinical utility, randomized trials start as high strength of evidence and observational studies start as low strength of evidence. In diagnostic studies, observational studies can start as high strength of evidence for diagnostic accuracy outcomes. The domains to be used for all KQs will be: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We will lower SOE grading when sensitivity analyses 1) show substantial difference in estimates derived from high or unclear risk of bias studies vs. estimates derived from studies at low risk of bias; or 2) when all the available studies (in a particular comparison) have high or unclear risk of bias. For outcomes measured on a standardized scale such as the asthma control composite scores, we will attempt to identify a minimally important difference (MID, defined as the smallest difference patients experience as an important effect) and use this value to help in making judgments about precision.²⁴ MID will be identified through relevant literature or consultation with the TEP. SOE grading will be also lowered when important heterogeneity is identified (I^2 squared values $> 50\%$ or heterogeneity test p value > 0.10). The importance of heterogeneity will be also judged based on clinical importance of differences across studies or the minimally important difference when available.

Based on this assessment and the initial study design, we will assign a strength of evidence rating as high, moderate, low, or ‘insufficient evidence to estimate an effect’. Independent reviewers, working in pairs, will grade the SOE and resolve the conflicts by discussion and consensus. We will produce summary of evidence tables that will provide for each comparison and for each outcome: data source, effect size, strength of evidence rating; and rationale for judgments made on each domain of evidence rating.

G. Assessing Applicability

We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.¹⁶ Applicability for each outcome will be summarized and presented qualitatively using the PICOTS framework. We will focus on whether the populations, interventions, and comparisons in existing studies are representative of current practice. We will select a limited number of the most important factors that may affect applicability (e.g., population of the studies may be different from that commonly seen in practice) and systematically abstract such factors and evaluate their impact on how applicable the evidence is to the question of interest. We will report any limitations in applicability of

individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables. Research gaps in the topic area will be reported by KQ.

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VI. Definition of Terms

ACQ	Asthma Control Questionnaire
ATS	American Thoracic Society
DOR	Diagnostic Odds Ratio
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
GINA	Global Initiative for Asthma
MID	Minimally Important Difference
NICE	National Institute for Health and Care Excellence
NHLBI	National Heart, Lung, and Blood Institute
KQ	Key Question
logDOR	Log Transformed Diagnostic Odds Ratio
RCT	Randomized Controlled Trial
TEP	Technical Expert Panel

VII. Summary of Protocol Amendments

No protocol amendments to date.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants. Further refinement will be done based on feedback from the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not conduct analysis of any kind nor do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

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XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).